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(54) **Catalytic decarboxylative cross-ketonisation of aryl- and alkylcarboxylic acids using iron catalysts**

(57) In the presence of catalytic amounts of magnetite nanopowder, mixtures of aromatic and aliphatic carboxylic acids are converted selectively into the corresponding aryl alkyl ketones. As by-products, only carbon dioxide and water are released. This catalytic cross-ketonisation allows the regioselective acylation of aromatic systems and, thus, represents a sustainable alternative to Friedel-Crafts acylations.

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Description

[0001] The present invention pertains to a method to prepare Aryl- and Alkylcarboxylic Acids using Fe-catalysts.

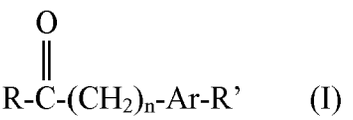
[0002] Aryl alkyl ketones are among the most important synthons in the industrial manufacture of commodities, fine chemicals, and pharmaceuticals. Simple derivatives, at early stages of the chemical value creation chain, are synthesised almost exclusively via Friedel-Crafts acylation of arenes, because the low cost of this reaction is unrivalled to date. However, two main issues are associated with this approach. Its low regioselectivity leads to the co-manufacture of large amounts of isomeric byproducts, and the use of acyl chlorides as starting materials activated with super-stoichiometric amounts of salt mediators (e.g., $AlCl_3$) is responsible for the formation of enormous quantities of salt waste.

[0003] Regioselective and less waste-intensive acylations, e.g., cross-couplings of sensitive aryl metal reagents with either preformed or in situ-generated carboxylic acid derivatives are widely used to access higher-value synthetic intermediates. However, their high cost precludes their application in the manufacture of base chemicals. This is also the case for alternative approaches, such as Heck-type reactions, or the Pd-catalysed decarboxylative cross-coupling of alpha-oxocarboxylate salts with aryl halides.

[0004] Thus, a need remained for a broadly applicable, regioselective and waste-minimised aryl alkyl ketone synthesis starting from simple, inexpensive, and widely available chemicals.

[0005] As a solution to this long-standing problem, a catalytic process in which two different carboxylic acids are cross-coupled under release of CO_2 and water, to selectively give the aryl alkyl ketones.

[0006] A first embodiment of the present invention pertains therefore to a method for the preparation of alkylarylketones according to the general formula (I)



$$R\text{-}C(=O)\text{-}(CH_2)_n\text{-}Ar\text{-}R' \qquad (I)$$

wherein R stands for a saturated or unsaturated, branched or linear alkyl or alkenyl moiety with 1 to 22 C-atoms, or an aromatic or hetero aromatic moiety with at least 5 C-atoms; Ar stands for an aromatic moiety, and R' represents a hydrogen atom, or a saturated or unsaturated, branched or linear alkyl or alkenyl moiety with 1 to 22 C-atoms, and n is Zero or a number of 1 to 4; comprising the steps

i) providing a blend of

(a) an aromatic monocarboxylic acid
(b) a second monocarboxylic acid, selected from benzylic or aliphatic monocarboxylic acids, or mixtures thereof, and
(c) an iron containing catalyst, and
(d) a non-aqueous solvent;

ii) heating said blend to a temperature of at least 220 ˚C for at least 10 h and continuously remove water and CO_2 from the blend during the reaction takes place,
iii) after the reaction is terminated, the blend is distilled under reduced pressure and the reaction product is obtained in the distillate;

whereby the catalyst (c) comprises Fe^{2+} species or a Fe^0 precursor.

[0007] In a decarboxylative cross-ketonisation according to the present invention, the carboxylate groups would predefine the position of bond formation, potentially allowing a selective synthesis of any desired regioisomer. If mediated by catalytic amounts of an inexpensive metal with high selectivity for hetero-over homocoupling, the overall process would be advantageous both from economical and ecological standpoints. The decarboxylative homoketonisation of aliphatic carboxylic acids is an established strategy for the preparation of symmetrical dialkyl ketones or cyclic alkanones.

[0008] The selection of a proper catalyst (c) is the main feature of the present invention. First, it must be a catalyst, irrespectively of its physical form (solid, liquid) containing a Fe^{2+} species or starting from a Fe^0 precursor.

[0009] This catalyst should be preferably used in solid form, for example as a powder. It is also beneficial to select those catalyst powders, having an average particle size of 1 - 500 nm, preferably with an average particle size of 1 - 50 nm and most preferable from 1 to 5 nm.

[0010] It is further an advantage to use a catalyst comprising a mixture of Fe^{2+} / Fe^{3+} species, and especially preferred

are a mixed Fe^{2+}/Fe^{3+} oxides. An example for such a mixed oxide is magnetite. Magnetite is a ferrimagnetic mineral with chemical formula Fe_3O_4, one of several iron oxides and a member of the spinel group. The chemical IUPAC name is iron(II,III) oxide and the common chemical name ferrous-ferric oxide. The formula for magnetite may also be written as $FeO \cdot Fe_2O_3$, which is one part wüstite (FeO) and one part hematite (Fe_2O_3). This refers to the different oxidation states of the iron in one structure, not a solid solution. A useful catalyst is a commercially available PVP stabilized magentite nanopwoder with an average particle size of 25 - 40 nm. The catalyst is used preferably in amounts from 5 mol% Fe^{2+} to 15 mol% Fe^{2+}, calculated on the mols of all carboxylic acids (a) and (b) in the reaction blend.

[0011] The aromatic monocarboxylic acid (a) is one substrate for the method of the present invention. It is essential that this acid contains at least one aromatic part or moiety. Various known aromatic monocarboxylic acids are suitable in the method of the present invention. The term aromatic will also include heterocyclic aromatic substrates. Compound (a) is preferably selected from the group benzene monocarboxylic acid, toluene monocarboxylic acid, halogen benzene monocarboxylic acids, halogen toluene monocarboxylic acids, alkoxy benzene monocarboxylic acid, dialkylamino benzene monocarboxylic acid, hydroxy benzene monocarboxylic acid, trifluoromethane benzene monocarboxylic acid or heteroaromatic monocarboxylic acids as furanyl monocarboxylic acid or thiophenyl monocarboxylic acid or polycyclic monocarboxylic acid as naphthalene monocarboxylic acid or any mixtures of these acids.

[0012] The second monocarboxylic acid (b) is selected from either benzylic or aliphatic monocarboxylic acids. The preferably selected substrates of type (b) are chosen from benzylic monocarboxylic acid or linear or branched C8-C22 fatty acids. For the sake of it is noted that the benzylic acid (b) must be structurally different to aromatic acid (a).

[0013] It was found that good results will be achieved if the mol ratio of (a) to (b) is in the range from 1 : 2 to 2 : 1. However, if almost equimolar mixtures of aromatic and aliphatic carboxylic acids are subjected to the above catalysts, dialkyl and aryl alkyl ketones are obtained at least in a 1: 9 ratio. An especially preferred ratio is in the range from 1.5 : 1 to 1.1 : 1 and particularly 1.2 : 1.

[0014] The presence of a non-aqueous solvent (d) is also compelling. Examples of proper solvents are sulfolane, tetraglyme, N-methyl-2-pyrrolidone or a eutectic mixture of diphenylether and biphenyl (Dowtherm®A). Other suitable solvents are selected from quinoline, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone trichlorobenzene, 1,4-butandiole, tetradecane, mineral oil, naphthalene or an eutectic mixture of diphenylether and biphenyl. Mixtures of the above mentioned solvents are also suitable.

[0015] The reaction is carried out at elevated temperatures, which is 200 ˚C and higher. The temperature during the reaction step ii) is kept preferably between 250 and 380 ˚C, more preferably between 270 and 340 ˚C. It is further an object to carry out the reaction using elaborate reaction technology such as gas phase reactions above 400 ˚C, or continuous flow reactors, but it is also possible to carry out the reaction at lower temperature then 400 ˚C in the condensed state.

[0016] Due to the probably detrimental effect of oxygen it is preferred to carry out the reaction under oxygen-free conditions, which means to apply a N_2 or Ar-atmosphere.

Examples

Synthesis of 2-phenyl-l-(3-tolyl)-ethanone

[0017] An oven-dried Schlenk flask was charged with magnetite nanopowder (< 50 nm, 590 mg, 98% purity, 2.50 mmol), 3-toluic acid (8.17 g, 60.0 mmol), phenylacetic acid (6.88 g, 99% purity, 50.0 mmol), and Dowtherm® A (100 mL).

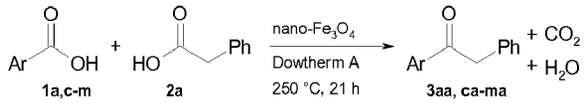
[0018] The apparatus was evacuated and flushed with nitrogen three times. The reaction mixture was heated to reflux (250 ˚C) overnight in a metal bath, while continuously removing CO_2 and water in a slow stream of nitrogen. The mixture was then distilled trap-to-trap (60-110 ˚C, 10-3 mbar) to give a clear, yellow distillate and dark brown residue. Compound 3aa was separated from Dowtherm® A

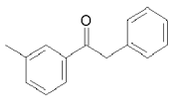
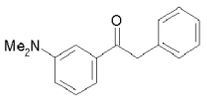
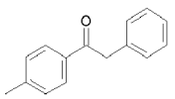
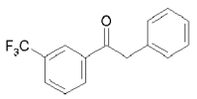
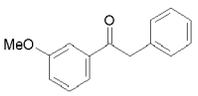
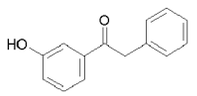
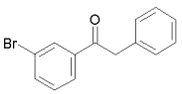
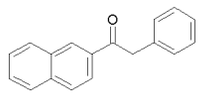
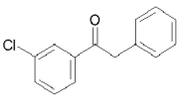
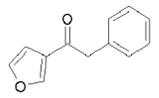
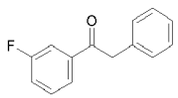
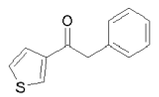
[0019] A by fractional distillation over a Vigreux column (Dowtherm® A: 55-60 ˚C, 10-3 mbar) and obtained as a pale yellow oil that solidified to an off-white solid upon cooling (100-105 ˚C, 10-3 mbar, 8.43 g, 80%, as a 10:1 mixture with 1,3-diphenylacetone).

[0020] For spectroscopic characterization, the product was further purified by column chromatography (SiO_2, ethyl acetate/hexane gradient). The spectroscopic data matched those reported in the literature for 2-phenyl-1-(3-tolyl)-ethanone (CAS 95606-81-8) [compound (3aa) in table 1].

[0021] Further examples with different aromatic carboxylic acids where conducted. The different products are shown in the following table 1:

Table 1



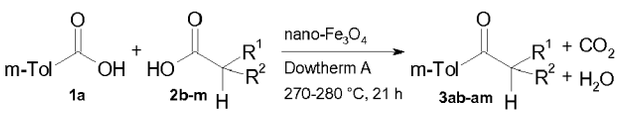
product	yield [%]	product	yield [%]
 **3aa**	80	 **3ha**	43
 **3ca**	65	 **3ia**	83
 **3da**	69	 **3ja**	27
 **3ea**	69	 **3ka**	80
 **3fa**	83	 **3la**	32
 **3ga**	78	 **3ma**	64[a]

Conditions: 1 20 mmol **1**, 100 mmol **2a**, 0 05 mmol Fe_3O_4, 21 h, 250 ˚C, 2 mL Dowtherm A, isolated yields [a] 0 07 mmol Fe_3O_4

[0022] According to the procedure as described in connection with compound 3aa reaction between aromatic monocarboxylic acids (in particular 3-methylbezene monocarboxylic acid) with different non aromatic acids of type (b) were conducted.

[0023] The results are shown in the table 2:

Table 2:



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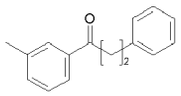
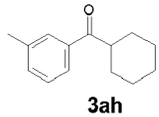
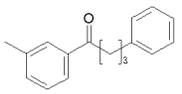
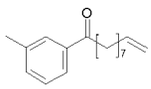
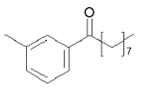
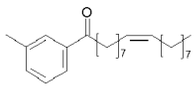
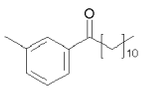
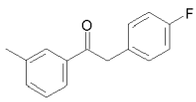
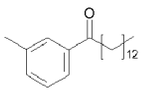
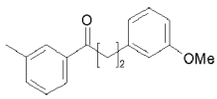
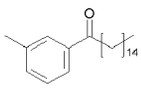
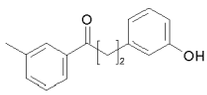
 **3ab**	78	 **3ah**	53[a]

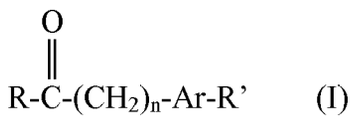
(continued)

product	yield [%]	product	yield [%]
 **3ac**	80	 **3ai**	51[b]
 **3ad**	86	 **3aj**	70
 **3ae**	85	 **3ak**	76[c]
 **3af**	76	 **3al**	59
 **3ag**	74	 **3am**	41

Conditions: 1 20 mmol **1a**, 1 00 mmol **2**, 0 07 mmol Fe_3O_4, 280 ˚C, 21 h, 2 mL Dowtherm A, isolated yields [a] 72 h [b] Mixture of isomers [c] 270 ˚C

Claims

1. A method for the preparation of alkylarylketones according to the general formula (I)



$$R\text{-}C(=O)\text{-}(CH_2)_n\text{-}Ar\text{-}R' \qquad (I)$$

wherein R stands for a saturated or unsaturated, branched or linear alkyl or alkenyl moiety with 1 to 22 C-atoms, or an aromatic or hetero aromatic moiety with at least 5 C-atoms; Ar stands for an aromatic moiety, and R' represents a hydrogen atom, or a saturated or unsaturated, branched or linear alkyl or alkenyl moiety with 1 to 22 C-atoms, and n is zero or a number of 1 to 4; comprising the steps

i) providing a blend of

(a) an aromatic monocarboxylic acid
(b) a second monocarboxylic acid, selected from benzylic or aliphatic monocarboxylic acids, or mixtures thereof, and
(c) an iron containing catalyst, and
(d) a non-aqueous solvent;

ii) heating said blend to a temperature of at least 220 ˚C for at least 10 h and continuously remove water and CO_2 from the blend during the reaction takes place,
iii) after the reaction is terminated, the blend is distilled under reduced pressure and the reaction product is obtained in the distillate;

characterized in that the catalyst (c) comprises a Fe^{2+} species or a Fe^{0} precursor.

2. A method according to claim 1, **characterized in that** the catalyst (c) is used in the form of a powder with an average particle size in the range of 1 - 500 nm, preferably with an average particle size of 1 - 50 nm, and preferably 1-5 nm.

3. A method according to at least one of the preceding claims, **characterized in that** the catalyst (c) comprises a mixture of Fe^{2+} / Fe^{3+} species.

4. A method according to at least one of the preceding claims, **characterized in that** the catalyst is a mixed Fe^{2+}/Fe^{3+} oxide.

5. A method according to at least one of the preceding claims **characterized in that** the catalyst (c) is used in amounts from 5 mol% Fe^{2+} to 15 mol% Fe^{2+}, calculated on the mols of all carboxylic acids (a) and (b) in the reaction blend.

6. A method, according to at least one of the preceding claims, **characterized in that** the monocarboxylic acid (a) is selected from the group benzene monocarboxylic acid, toluene monocarboxylic acid, halogen benzene monocarboxylic acids, halogen toluene monocarboxylic acids, alkoxy benzene monocarboxylic acid, dialkylamino benzene monocarboxylic acid, hydroxy benzene monocarboxylic acid, trifluoromethane benzene monocarboxylic acid or heteroaromatic monocarboxylic acids as furanyl monocarboxylic acid or thiophenyl monocarboxylic acid or polycyclic monocarboxylic acid as naphthalene monocarboxylic acid.

7. A method according to at least one of the preceding claims, **characterized in that** the second monocarboxylic acid (b) is benzyl monocarboxylic acid.

8. A method according to at least one of the preceding claims, **characterized in that** the second monocarboxylic acid (b) is a saturated or unsaturated C8-C22 fatty acid, a branched or alicyclic monocarboxylic acid without heteroatoms or an alicyclic monocarboxylic acids containing heteroatoms for example oxygen or sulfur atoms, an aryl alkyl monocarboxylic acid as hydroxyphenyl alkyl monocarboxylic acid, alkoxyphenyl alkyl monocarboxylic acid, halogenphenyl alkyl monocarboxylic acid, a polycyclic monocarboxylic acid as naphthyl alkyl monocarboxylic acid.

9. A method according to at least one of the preceding claims, **characterized in that** the non-aqueous solvent is selected from sulfolane, tetraglyme, n-methyl-2-pyrrolidone, quinoline, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone trichlorobenzene, 1,4-butandiole, tetradecane, mineral oil, naphthalene or an eutectic mixture of diphenylether and biphenyl.

10. A method according to at least one of the preceding claims, **characterized in that** the temperature during step ii) is kept between 250 and 380 ˚C, preferably between 270 and 340 ˚C.

11. A method according to at least one of the preceding claims, **characterized in that** the reaction step (ii) is carried out for a period of time of 10 h to 24 h.

12. A method according to at least one of the preceding claims, **characterized in that** the reaction is carried out under a N_2 or Ar-atmosphere.

13. A method according to at least one of the preceding claims **characterized in that** the mol ratio of (a) to (b) is in the range from 1 : 1 (1:2) to 5 : 1, preferred is a ratio of 1.2 : 1.

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EUROPEAN SEARCH REPORT

Application Number
EP 10 19 4330

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	GRANITO, CHARLES ET AL: "Decarboxylation studies. II. Preparation of alkyl phenyl ketones", JOURNAL OF ORGANIC CHEMISTRY , 28, 879-81 CODEN: JOCEAH; ISSN: 0022-3263, 1963, XP002620841,	1,2,5-13	INV. C07C45/48 C07C225/22 C07C49/76 C07C49/813 C07C49/83
Y	* the whole document *	3,4	C07C49/784 C07C49/794

X	WANG SHUQING ET AL: "Study on synthesis of m-chloropropiophenone from m-chlorobenzoic acid and propionic acid", JINGXI SHIYOU HUAGONG = SPECIALTY PETROCHEMICALS, ZHONGGUO SHIYOU HUAGONG ZONGGONGSI, CN, no. 4, 1 January 2005 (2005-01-01), pages 1-3, XP008132676, ISSN: 1003-9384	1,2,5-12	C07C49/84 C07D307/46 C07D333/22
Y	* abstract *	3,4	

X	DATABASE WPI Week 201067 Thomson Scientific, London, GB; AN 2010-L41304 XP002620866, & CN 101 805 251 A (UNIV NANTONG) 18 August 2010 (2010-08-18)	1,2,5-12	TECHNICAL FIELDS SEARCHED (IPC) C07C C07D
Y	* abstract *	3,4	

Y	PESTMAN R ET AL: "Reactions of Carboxylic Acids on Oxides - 2. Bimolecular Reaction of Aliphatic Acids to Ketones", JOURNAL OF CATALYSIS, ACADEMIC PRESS, DULUTH, MN, US, vol. 168, no. 2, 1 June 1997 (1997-06-01), pages 265-272, XP004459599, ISSN: 0021-9517, DOI: DOI:10.1006/JCAT.1997.1624 * page 265, paragraph first *	3,4	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	9 February 2011	Patteux, Claudine

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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Y	CRESSELY J ET AL: "Evolution des especes carboxylates dans le cadre des syntheses CO-H2. Reduction de l'acide acetique sur systeme Co, Cu, Fe", MATERIALS CHEMISTRY AND PHYSICS, ELSEVIER, SWITZERLAND, TAIWAN, REPUBLIC OF CHINA, vol. 11, no. 5, 1 November 1984 (1984-11-01), pages 413-431, XP024148428, ISSN: 0254-0584, DOI: DOI:10.1016/0254-0584(84)90065-8 [retrieved on 1984-11-01] * page 416 - page 417 * * page 424 - page 429 * -----	3,4	
A	MAILHE M A: "Sur les catalyseurs des acides", BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, SOCIETE FRANCAISE DE CHIMIE. PARIS, FRANCE, vol. 4, no. 15, 1 January 1914 (1914-01-01), pages 321-326, XP008132613, ISSN: 0037-8968 * the whole document * -----	1-13	TECHNICAL FIELDS SEARCHED (IPC)

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